1/PART

The use of TNF antagonists as drugs for treating septic disorders

The present invention relates to the use of TNF antagonists for treating septic disorders.

It is known that the term tumor necrosis factor (TNF) embraces two cytotoxic factors (TNF-α and TNF-β) which are mostly produced by activated lymphocytes and monocytes.

EP 260 610 describes, for example, anti-TNF antibodies which are said to be usable for inactivating TNF in disorders associated with an increase in TNF in the blood, such as septic shock, transplant rejection, allergies, autoimmune diseases, shock lung, coagulation disturbances or inflammatory bone disorders.

In medical textbooks, septic disorders are defined as a collective term for clinical states in which agents causing inflammation, eg. bacteria, start from a focus and reach the blood stream, which initiates a wide range of subjective and objective pathological manifestations. It is further found that the clinical picture may vary widely depending on the type of causative agent, the responsivity of the body, the primary focus and the varying involvement of organs (Sturm et al. "Grundbegriffe der Inneren Medizin", 13th Edition, page 570, Gustav Fischer Verlag, Stuttgart, 1984).

A number of cytokines have been suggested to be involved in the complex pathophysiological process of sepsis. TNF in particular is, on the basis of data from animal experiments (Beutler et al., Science 229 (1985) 869-871), ascribed an important role in septic shock.

This eventually led to clinical studies being carried out on the treatment of sepsis patients with anti-TNF antibodies.

However, it was found in a recently published multicenter phase II study on the treatment of severe sepsis with a murine monoclonal anti-TNF antibody that the overall group (80 patients) did not benefit in terms of survival rate from the treatment with the antibody. Only the patients with elevated TNF concentrations in the circulation appeared to benefit in terms of the probability of survival from high-dose anti-TNF antibody administration (C.J. Fisher et al., Critical Care Medicine, Vol.

21, No.3, pages 318-327). There is also a reference in this study to a correlation between the plasma levels of TNF and IL-6.

The part played by the cytokine interleukin-6 (IL-6) in sepsis is unclear and contradictory. Elevated levels of IL-6 have been found in the serum of some sepsis patients (Hack et al., Blood 74, No. 5, (1989) 1704-1710).

Waage describes a correlation between the concentrations of the cytokines IL-6 and IL-8 and the severity of the shock, but they have no effect, either alone or in combination with TNF, in terms of mortality, on the development of a shock syndrome (Waage in "Tumor Necrosis Factors", ed. B. Beutler, Raven Press, New York, 1992, pages 275-283).

Some scientists have ascribed a beneficial role to IL-6 in septic shock because IL-6 inhibits, in the form of negative feedback control, the LPS-induced TNF production (Libert et al. in "Tumor Necrosis Factor: Molecular and Cellular Biology and Clinical Relevance", ed. W. Fiers, Karger, Basle, 1993, pages 126-131).

WO 95/00291 discloses TNF antagonists as medicines for treating sepsis in patients in whom the serum levels of interleukin-6 are 500 pg/ml or more.

However, it emerged from clinical studies that the treatment disclosed in WO 95/00291 was not always successful.

It is evident that there are cases of sepsis which can be treated successfully with TNF antagonists, while in other cases treatment with TNF antagonists is not successful and is in fact contraindicated.

It is an object of the present invention to identify, reliably and rapidly, those patients suffering from sepsis who can be successfully treated with TNF antagonists.

We have found that this object is achieved by using the following features to identify patients with septic disorders who can be treated successfully:

The serum level of interleukin-6 is increasing, ie. within a measurement period of at least 30 minutes the level measured at the later time is higher than the level measured first.

Patients suffering from sepsis and satisfying this criterion are very suitable for treatment with TNF antagonists.

The treatment is preferably carried out on patients whose serum level of interleukin-6 in the measurement period is at least 500 pg/ml. However, it may also be distinctly higher than this level and be up to the order of a few mg/ml.

In order to establish whether the serum level of interleukin-6 (IL-6) is increasing, it is necessary to carry out at least two IL-6 measurements.

The second, later measurement should be obtained within a period of from 30 minutes to 48 hours after the first IL-6 measurement (measurement period).

The measurement period is preferably 2 - 24, in particular 4 - 10, hours.

The patients to be treated are, as a rule, undergoing intensive medical treatment which sometimes does not permit strict measurement period limits to be complied with.

The extent of the rise in the serum level of IL-6 between the two measurements is not so crucial for the use according to the invention.

If the serum level of IL-6 does not increase or even falls during the measurement period, treatment with TNF antagonists is not recommended.

The serum concentrations of IL-6 can be determined by conventional detection methods such as RIA or ELISA. An example of a very suitable detection system is the IL-6-EASIA supplied by Medgenix.

The concentration of IL-6 can also be determined in an activity assay in which, for example, C-reactive protein is assayed.

Since different measurement methods or assay systems sometimes give different results for the same measurement, it is advisable either to use the same measurement method or assay system for

determining the IL-6 levels or, if different systems are used, to calibrate them against each other.

Suitable TNF antagonists are anti-TNF antibodies, TNF receptors or soluble fragments thereof, TNF-binding proteins or those TNF derivatives which still possess TNF receptor binding but no longer have any TNF activity. TNF antagonists of these types have the characteristic that they trap TNF which has already been produced and do not allow it to reach the TNF receptor or that they compete with the TNF for the receptor.

However, TNF antagonists which prevent the formation or release of TNF are also suitable for the use according to the invention. Substances of this type inhibit, for example, TNF gene expression or the release of TNF from precursor forms. Examples of suitable TNF antagonists are inhibitors of TNF convertase.

TNF-antagonistic activities have been described, for example, for xanthine derivatives, glucocorticoids, prostaglandin E 2, thalidomide, interleukin-4, interleukin-10, granulocyte stimulating factor (G-CSF), cyclosporin and α-antitrypsin. Thus compounds of these types are also suitable as TNF antagonists.

The TNF antagonists suitable for the use according to the invention are described, for example, by Mariott et al. DDT, Vol. 2, No. 7, July 1997 and in the literature cited therein.

Anti-TNF antibodies and fragments thereof are particularly preferred for the use according to the invention.

The anti-TNF antibodies suitable for the use according to the invention are known (EP 260 610, EP 351 789, EP 218 868). It is possible to use both polyclonal and monoclonal antibodies. Also suitable in addition are TNF-binding antibody fragments such as Fab or $F(ab')_2$ fragments or single-chain Fv fragments.

Humanized or human anti-TNF antibodies or their TNF-binding fragments are also very suitable because these molecules ought not to cause any anti-mouse antigenicity in human patients.

It is also possible to use mixtures of various anti-TNF antibodies or of anti-TNF antibodies and TNF receptor fragments as active ingredient.

The present invention includes pharmaceutical compositions which, besides nontoxic, inert pharmaceutically suitable carriers, comprise the anti-TNF antibodies, and processes for producing these compositions.

The anti-TNF antibodies are formulated in a way customary for biotechnologically produced active ingredients, as a rule as liquid formulation or lyophilisate (see, for example, Hagers Handbuch der pharmazeutischen Praxis, Vol. 2, 5th Edition, 1991, page 720, ISBN 3-540-52459-2). The pharmaceutical compositions mentioned above are produced in a conventional way by known methods, for example by mixing the active ingredient(s) with the carrier(s).

It has in general proven advantageous to administer the active ingredient(s) suitable for the use according to the invention in total amounts of about 0.1 to about 100, preferably 0.1 to 10, mg/kg of body weight every 24 hours, where appropriate in the form of several individual doses or as continuous infusion and, where appropriate, over a treatment period of several days to achieve the desired results. Administration can take place as brief intravenous infusion of the single doses or as continuous long-term infusion of the daily dose over 24 hours. A single dose preferably contains the active ingredient(s) in amounts of about 0.1 to about 10 mg/kg of body weight. However, it may be necessary to deviate from the stated dosages, in particular as a function of the age and size of the patient to be treated and the nature and severity of the underlying disorder, the nature of the composition and of the administration of the drug, and the period over which administration takes place.

The invention is illustrated further in the following example.

Example

Treatment of sepsis patients with a murine anti-TNF antibody fragment ($F(ab')_2$), called MAb 195F (INN: AFELIMOMAB).

In total, 251 patients with severe sepsis who where treated either with an anti-TNF antibody fragment (afelimomab) or as control patients were analyzed in a multicenter clinical study.

Of the 251 patients, 47 had an increasing and 178 had a decreasing serum level of IL-6.

The figure shows that a decrease in mortality can be achieved by the treatment in the group with increasing IL-6 level (55.6% mortality compared with 69% in the controls).

There is no evident success of treatment with MAb 195 F in the group where the serum level of IL-6 was falling; on the contrary, in fact an adverse effect of the treatment is evident (mortality 54.7% compared with 50.6% in the control group).

The treatment group received, in addition to the standard treatment of sepsis, the trial product afelimomab over a period of 3 days as a total of nine brief infusions lasting 15 minutes, each at intervals of eight hours, in a single dose of 1 mg/kg of body weight each time. The control group received in addition to the standard treatment of sepsis a pharmacologically inactive sham product (placebo) administered in the same regimen.

The result of this clinical study clearly demonstrates that the treatment of severe sepsis with anti-TNF antibodies is particularly successful when the sepsis patients who are treated have an increasing serum level of IL-6. Patients who have a falling serum level of IL-6 should accordingly not be treated with TNF antagonists.